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Provisional Peer-Reviewed Toxicity Values for

Benzyl alcohol
(CASRN 100-51-6)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR BENZYL ALCOHOL (CASRN 100-51-6)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths

and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

There is no assessment of benzyl alcohol on IRIS (U.S. EPA, 2008), and there is no RfD for benzyl alcohol on the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). The HEAST (U.S. EPA, 1997) lists subchronic and chronic RfD values for benzyl alcohol of 1×10^{0} and 3×10^{-1} mg/kg-day, respectively. The source document for these assessments is a Health and Environmental Effects Document (HEED) (U.S. EPA, 1989). The subchronic RfD is based on a NOAEL of 143 mg/kg-day in a 13-week study in rats (NTP, 1989); the reported critical effect is decreased body weight, and an uncertainty factor (UF) of 100 is used. The chronic RfD is based on a LOAEL of 286 mg/kg-day in a 2-year study in rats (NTP, 1989a); the reported critical effect is epithelial hyperplasia in the forestomach, and the UF was 1000. Other than the HEED discussed above, the CARA list (U.S. EPA, 1991, 1994) does not include any relevant documents. Benzyl alcohol was included in two reviews of benzyl derivatives prepared by the WHO Expert Committee on Food Additives (WHO, 2005; FAO/WHO, 1996). The Committee derived an ADI of 0–5 mg/kg for benzyl alcohol (WHO, 2005). The National Toxicology Program (NTP, 1989a) has conducted 16-day and 13-week oral studies and a 2-year oral exposure cancer bioassay of benzyl alcohol. Neither CalEPA (2008a,b) nor ATSDR (2008) has assessed the toxicity of benzyl alcohol.

An RfC for benzyl alcohol is not available on IRIS (U.S. EPA, 2008) or in the HEAST (U.S. EPA, 1997). The HEED (U.S. EPA, 1989) reported that there were no inhalation toxicity data in humans or animals at the time of publication. Occupational exposure limits for benzyl alcohol have not been derived by ACGIH (2008), NIOSH (2008), or OSHA (2008).

A cancer assessment for benzyl alcohol is not available on IRIS (U.S. EPA, 2008) or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). A Weight of Evidence classification for benzyl alcohol is not listed in the HEAST. Using the U.S. EPA (1986) guidelines, the HEED (U.S. EPA, 1989) assigned benzyl alcohol to Weight of Evidence Group D (not classifiable as to human carcinogenicity) in the executive summary and Group E (evidence of noncarcinogenicity) in the text. NTP (1989a) concluded that there was no evidence of carcinogenic activity in male or female rats or mice administered benzyl alcohol via oral gavage for 2 years. Benzyl alcohol is not included in the 11th Report on Carcinogens (NTP, 2005). The carcinogenicity of benzyl alcohol has not been assessed by IARC (2008).

Benzyl alcohol is used as a topical anesthetic and was shown to induce a spectrum of behavioral responses identical to ethyl alcohol intoxication. Benzyl alcohol is also used as a preservative in medicinal products and was identified as a component associated with brain hemorrhage in infants and neonates (NTP, 1989a).

Literature searches were conducted from 1960s through May 28, 2009 for studies relevant to the derivation of provisional toxicity values for benzyl alcohol. Databases searched include MEDLINE, TOXLINE (with NTIS), BIOSIS, TSCATS/TSCATS2, CCRIS, DART, GENETOX, HSDB, RTECS, Chemical Abstracts, and Current Contents (last 6 months). An OECD SIDS Initial Assessment Report (OECD, 2001) and a Cosmetic Ingredient Review Expert Panel Report (Nair, 2001) were also consulted for relevant information. An updated literature search was performed in MEDLINE, TOXLINE (with NTIS), BIOSIS, PUBMED, and Current Contents from October 2008 to May 2009.

REVIEW OF PERTINENT DATA

Human Studies

Available data in humans are limited to case reports where exposure to benzyl alcohol occurred with other solvents or when administered as a bacteriostatic agent with other medications. These reports provided no dose-response in humans for quantitative assessments. Workers occupationally exposed for an undetermined duration to a high vapor concentration of a mixture containing benzyl alcohol, benzene, and ester solvents reported temporary headaches, vertigo, nausea, diarrhea, and weight loss (Treon and Stasik, 1983). Also, several reports describe toxicity in preterm neonates exposed intravascularly to solutions that contained benzyl alcohol as a preservative (Brown et al., 1982; Gershanik et al., 1982). Brown et al. (1982) gave details of 10 of 16 low birth weight infants (<1250 g) who died following exposure to bacteriostatic normal saline containing benzyl alcohol at a dose between 130 and 405 mg/kg-day. Symptoms of toxicity were observed between Days 2 and 4 of administration and included slowly progressive bradycardia, often with gasping respiration (resulting in the name "gasping syndrome"), seizures, unresponsiveness, and extremely depressed EEGs characteristic of progressive metabolic acidosis. Gershanik et al. (1982) reported that 10 low birth weight or premature infants developed gasping syndrome following hospitalization and exposure to benzyl alcohol intravenously in medications. Effects were similar to those reported by Brown et al. (1982). Infants that developed gasping syndrome received benzyl alcohol doses ranging from 99–234 mg/kg-day. A matched control group of infants who did not develop gasping syndrome received 27–99 mg/kg-day of benzyl alcohol intravenously. Menon et al. (1984) and Benda et al. (1986) reported a possible association between benzyl alcohol and brain hemorrhages in low birth weight infants given medicine with benzyl alcohol added as a preservative. Benda et al. (1986) also reported significant ($p < 0.001$) decreases in the incidences of cerebral palsy and developmental delay in surviving low birth weight infants after benzyl alcohol use was discontinued in a neonatal intensive care unit. Hiller et al. (1986) reported a strong association with benzyl alcohol exposure and gasping syndrome and death in a large cohort of 61 low birth weight infants born prematurely. Significant decreases in neurotoxicity and mortality were reported in infants who did not receive benzyl alcohol compared to those who received. Neurotoxicological findings, such as kernicterus, intraventricular hemorrhage, and mortality in preterm infants have also been reported in other case studies (Jardine and Rogers, 1989).

Animal Studies

McClogskey et al. (1986) reported minimal toxic effects in CD mice to benzyl alcohol at doses below 800 mg/kg in a 4-hour observation period whereas mortality (LD50) was observed at 650 mg benzyl alcohol dose administered intraperitoneally to adult and neonatal mice during a seven day observation period. In the metabolism part of this study, the authors observed that the toxicity was related to the parent compound not the metabolite of benzyl alcohol. The subchronic and chronic toxicity and carcinogenicity of benzyl alcohol following oral exposure has been studied by NTP (1989a). Several screening assays that investigated the developmental toxicity of orally administered benzyl alcohol were also conducted (York et al., 1988; York et al., 1986; Hazelden, 1983; Hardin et al., 1987). Subchronic/chronic studies evaluating the toxicity of benzyl alcohol following inhalation exposure were unavailable.

In 13-week repeated-dose studies, groups of rats and mice (10 per sex and dose) were administered 0, 50, 100, 200, 400, or 800 mg/kg-day of benzyl alcohol in corn oil 5 days/week via oral gavage (NTP, 1989a). Dose selection was based on results from 16-day studies in rats and mice that observed treatment-related effects (including increased mortality, lethargy, decreased mean final body weight, and presence of blood around the nose, mouth, GI tract, and urinary tract) at ≥1000 mg/kg-day. In the 13-week studies, animals were observed twice daily for signs of toxicity and mortality. Animals were weighed individually at the beginning and end of the studies and were weighed as groups weekly during the study. All animals were necropsied after 13 weeks of treatment (or killed *in extremis* during the study), and unspecified tissues were microscopically examined from all control and high-dose animals. The brain was microscopically examined at 0, 400, and 800 mg/kg-day in rats and mice and in all mice that died prior to the scheduled sacrifice. No clinical pathology examinations (e.g., clinical chemistry, hematology, urinalysis) were conducted.

In rats, 8/10 males and 2/10 females in the 800 mg/kg-day group died; 4/10 of the deaths in males and 1/10 deaths in females were attributed to gavage error (NTP, 1989a). Signs of neurotoxicity (including staggering, labored breathing, and lethargy) were observed in male and female rats at 800 mg/kg-day, and 5/10 males at this dose were observed with blood around the nose and mouth after 8 weeks of treatment. No toxicologically significant decrease in final mean body weight was observed at any dose. No treatment-related gross lesions were reported. Histopathological effects attributable to treatment at 800 mg/kg-day included necrosis of the dentate gyrus of the hippocampus (9/9 males; 7/7 females); skeletal muscle necrosis (5/10 males); thymic congestion, hemorrhage, and atrophy (8/10 males); and renal nephrosis (6/9 males) similar to spontaneous age-related renal disease. The NTP report states that these lesions were not observed at lower doses. Therefore, treatment-related effects (mortality and neurotoxicity) were only observed at the high dose (800 mg/kg-day) in rats administered benzyl alcohol for 13 weeks. The NOAEL and FEL values in rats are 400 mg/kg-day and 800 mg/kg-day, respectively.

In mice, there was no clear dose-related trend in mortality incidence (NTP, 1989a). Final mean body weights of mice in all treatment groups were within 10% of controls. In the first 2 weeks of the study, male and female mice staggered after receiving 800 mg/kg-day of benzyl alcohol. No other treatment-related clinical signs were observed. No gross or microscopic lesions attributable to treatment were seen in mice at any dose. Interstitial pneumonia observed in all groups was consistent with Sendai infection. Treatment-related effects in this study included clinical observation of staggering in high-dose males and females; no effects were

observed at 400 mg/kg-day. Therefore, the NOAEL and LOAEL values in mice are 400 mg/kg-day and 800 mg/kg-day, respectively.

In the 2-year studies conducted by NTP (1989a), technical-grade benzyl alcohol (99% pure) dissolved in corn oil was administered by gavage 5 days/week, for 103 weeks, to 50 male and female F344/N rats at concentrations of 0, 200, or 400 mg/kg and $B6C3F_1$ mice at concentrations of 0, 100, or 200 mg/kg. Mice were unintentionally given α-methylbenzyl alcohol for 4 days during Week 80 with no observed toxicological syndromes. Animals were observed twice daily for signs of toxicity. Body weight was recorded at study initiation, weekly for 12 weeks, then monthly thereafter. After 2 years of treatment, all animals were necropsied, and a comprehensive set of tissues was microscopically examined from all female rats, control and high-dose male rats and mice, male rats and mice that died prior to 22 months of treatment, and male rats and mice with gross lesions. In addition, the pituitary gland and testes were microscopically examined in low-dose male rats; the adrenal gland, brain, kidney, liver and lungs were examined in low-dose male mice; and the brain, liver, spleen, and uterus were examined in low-dose female mice. When mortality at the high dose was ≥15% above the control group for a particular sex and species, then a complete histopathological examination was performed on all animals of that sex and species in the low- and high-dose groups. Clinical chemistry, hematology, urinalysis, or ophthalmology parameters were not evaluated.

Survival of the benzyl alcohol treated female rats was significantly lower than controls after Week 50 in high-dose animals and, after Week 71, in low-dose animals (NTP, 1989a). Many of the deaths were attributed to gavage error (1, 17, and 13 in the control, low-, and high-dose groups, respectively); however, there was an apparent dose-response trend in nonaccidental deaths in females (13/50, 16/50, and 20/50, respectively, at 0, 200, and 400 mg/kg-day). Because of the high incidence of gavage-related deaths, it is not clear if the apparent increase in nonaccidental mortality in treated female rats was related to benzyl alcohol toxicity. In males, an apparent dose-related increase in gavage-related deaths was observed (4/50, 8/50, and 14/50 at 0, 200, and 400 mg/kg-day, respectively); however, survival curves in males were similar in both treated groups compared with controls. No effects on body weight or incidences of clinical signs of toxicity were observed.

High-dose male rats were observed with a higher incidence of epithelial hyperplasia in the forestomach than controls (0/48, 0/19, and 4/50 at 0, 200, and 400 mg/kg-day, respectively) (NTP, 1989a). It is possible that this observation was related to benzyl alcohol treatment because benzyl acetate, which is metabolized to benzyl alcohol (NTP, 1989a), induced forestomach hyperplasia and squamous cell neoplasms in male and female mice dosed via oral gavage at 1000 mg/kg-day (molar equivalent to 720 mg/kg-day of benzyl alcohol) (NTP, 1986), but not in male or female rats or mice exposed at up to 350 mg/kg-day (molar equivalent to 252 mg/kg-day benzyl alcohol) in the diet for 2 years (NTP, 1993). Because benzyl acetate is metabolized to benzyl alcohol (NTP, 1989a), these data provide suggestive evidence that the forestomach is a potential target organ for benzyl alcohol in gavaged animals. However, the incidence of forestomach hyperplasia in high-dose benzyl alcohol treated male F344/N rats (4/50) was low. Increased incidences of microscopic lesions of the respiratory tract, larynx, and lungs were also observed in treated rats; however, these effects appear to have been caused by gavage error or by reflux of the gavage material and aspiration into the lungs due to the anesthetic properties of the test substance. High-dose rats were also observed with an increased incidence of cataracts and retinal atrophy, but this was attributed to those animals being housed

in cages on the top racks, permitting greater exposure to fluorescent lighting. The data from this study indicate that there were no toxic effects that were associated with benzyl alcohol administration to male or female rats at any dose; therefore, the NOAEL in rats observed in this study is 400 mg/kg-day, and a clear LOAEL is not established. There is some uncertainty, however, as meaningful interpretation of the mortality data is not possible due to the high rate of gavage errors—particularly in females. Thus, the data cannot be used for dose-response assessments.

In mice, no effects on survival, clinical signs of toxicity, or body weight were observed (NTP, 1989a). High-dose male and female mice had an increased incidence of corpora amylacea (incidence of 15/49, 21/48, and 22/50 in males and 14/50, 15/48, and 25/50 in females in the control, low-, and high-dose groups, respectively). The lesion was described as consisting of "one or several small foci of mineralization in the thalamus" and was noted to be a common, spontaneously occurring lesion. Inspection of 2-year studies published in 1989 by the National Toxicology Program indicates that the incidences of corpora amylacea in the 2-year benzyl alcohol study in mice were within the vehicle control incidence of brain mineralization in mice in these studies (NTP, 1989e,f). Therefore, it does not appear that this lesion was likely related to benzyl alcohol treatment. There was also an increased incidence ($p = 0.044$ by the life table and incidental tumor tests) in adrenal cortex adenomas in high-dose male mice (adjusted terminal rates of 0/33, 0/30, and 3/35 in the control, low-, and high-dose groups, respectively). The incidence at the high dose, however, was within the historical control incidence and was, therefore, not attributed to benzyl alcohol treatment. Overall, no treatment-related effects were observed in this study at any dose. Therefore, the NOAEL in mice is 200 mg/kg-day (143 mg/kg-day when adjusted for a 5 day/week dosing schedule), the highest dose tested, and a LOAEL is not achieved.

Interpretation of the 2-year study in mice is unclear because it appears that this species, like rats, could have been given doses higher than 200 mg/kg-day—the highest dose tested. The study authors indicated that mice were given lower doses than rats based on reduced relative body weight gain observed at ≥400 mg/kg-day and on the anesthetic properties of benzyl alcohol, which may have contributed to the gavage related deaths in the 13-week studies (NTP, 1989a). However, the 13-week studies appeared to indicate that rats were more sensitive to benzyl alcohol toxicity than mice, and rats tolerated doses up to 400 mg/kg-day for two years; therefore, it appears that mice could have tolerated doses substantially higher than 200 mg/kg-day for 2 years.

The developmental toxicity of benzyl alcohol has been evaluated in several screening assays (Hazelden, 1983; York et al., 1986; Hardin et al., 1987;York et al., 1988). In one study, groups of 50 SPF, pregnant female CD-1 mice, 6–8 weeks old, were gavaged with benzyl alcohol in distilled water at 0 or 750 mg/kg-day on gestation days (GDs) 6–13 (presence of vaginal sperm plug = Day 0) (Hardin et al., 1987; Hazelden, 1983). Mice were observed twice daily for clinical signs of toxicity and mortality during treatment, once daily during GDs 14–17, and twice daily after GD 18 for signs of parturition. Mice that died early were necropsied for the purpose of excluding gavage error as a cause of death. Body weights of the dams were recorded at study initiation, on GDs 6 and 17, and on Day 3 postpartum. Number of pups/litter and total litter weights were recorded within 12 hours of parturition (Day 1 postpartum) and again 48 hours later. The following parameters were evaluated: maternal mortality and weight change, number of viable fetuses, number of live births per litter, and pup birth weight, percent survival

and weight gain. Nineteen of the 50 treated mice died. Reproductive and gestation indices and mean gestation lengths were not significantly different in treated and control mice. Maternal body weight was significantly less than controls throughout the exposure period and on Day 3 postpartum. Other signs of maternal toxicity included increased mortality, cyanosis, dyspnea, hypothermia, behavioral pathologies, and piloerection, which could lead to mortality. Mean litter weight was also significantly less than controls on Days 1 and 3 postpartum. A NOAEL is not achieved.

In a similar study, York et al. (1986) administered benzyl alcohol by oral gavage to 50 mice/dose at 0 or 550 mg/kg-day on GDs 6–15. All dams were allowed to deliver naturally. Body weight was recorded daily and all animals were observed for clinical signs of toxicity and mortality daily throughout treatment until Day 3 postpartum. No clear effects on mortality, clinical signs of toxicity, maternal body weight, or body weight gain, gestation index, average number of live pups per litter, postnatal survival, or pup body weight on Days 0 and 3 postpartum were observed. The NOAEL in this study is 550 mg/kg-day, the only dose tested.

In another preliminary, short-term developmental toxicity test in mice, benzyl alcohol was given a score of intermediate priority classification or "no decision" when rated relative to five indices of potential developmental toxicity (i.e., the proportion of pregnant survivors that produced a litter of at least one live born pup, average litter sex ratio and pup weight at birth, and average pup survival and weight gain) to 3 days of age (York, et al., 1988). No other information was given.

Taken together, the available data are not adequate to fully evaluate the ability of benzyl alcohol to induce developmental toxicity because the presence of visceral or skeletal malformations are not systematically evaluated in any of the studies. Reproductive organs in the NTP (1993) studies were unaffected by benzyl alcohol in both mice and rats. The data generated at NIOSH laboratory (York et al., 1986; Hardin et al., 1987) and the extensive evaluation reported by the Flavor and Extract Manufacturers Association (FEMA) expert panel (Adams et al., 2005) do not provide adequate information to evaluate developmental toxicity of benzyl alcohol.

Other Studies

Benzyl alcohol did not induce reverse mutations in seven *Salmonella typhimurium* tester strains or in two strains of *E. coli* with or without addition of an exogenous metabolic activation system (S9) (Fluck et al., 1976; Florin et al., 1980; Ishidate et al., 1984; Mortelmans et al., 1986; Rogan et al., 1986; NTP, 1989a). Benzyl alcohol at cytotoxic concentrations produced forward mutations (triflourothymidine resistance) in the mouse L5178Y/TK+/- lymphoma assay without S9 addition but not with S9 (NTP, 1989a). The chemical also caused DNA damage in *Bacillus subtilis* (Yoo, 1986; Kuroda et al., 1984). Benzyl alcohol did not induce DNA damage in human alveolar cells (Waters et al., 1982). Benzyl alcohol was not positive in an in vitro chromosomal aberrations test in Chinese Hamster Lung cells without metabolic activation (Ishidate et al., 1988); in Chinese Hamster ovary (CHO) cells, benzyl alcohol induced chromosomal aberrations in the presence of S9 mix—but not without S9 (NTP, 1989a). An equivocal increase in sister chromatid exchanges was observed in CHO cells in the presence or absence of S9 activation (NTP, 1989a). The substance did not induce micronucleus formation in mice in vivo (Hayashi et al., 1988). Overall, benzyl alcohol has produced mixed results in genotoxicity assays; however, the data suggest that benzyl alcohol is not likely a genotoxic agent.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR BENZYL ALCOHOL

Available human studies have several limitations, such as exposure as mixtures and exposure as bacteriostatic agents with other medications. Benzyl alcohol was the subject of subchronic and chronic animal studies conducted by the National Toxicology Program (1989a), but no other relevant repeated-dose toxicity studies were located. In the subchronic studies (NTP, 1989a), treatment-related effects were only observed at the high dose, 800 mg/kg-day, and included mortality in male and female rats, increased incidences of clinical signs of neurotoxicity (including staggering, labored breathing, and/or lethargy) in male and female rats and mice, presence of blood around the nose and mouth in male rats, necrotic lesions of the brain in male and female rats, thymic congestion, hemorrhage, and atrophy in male rats, and nephrosis in male rats. Although these effects in rats may lead to FEL, there were several uncertainties, possibly due to significant gavage errors. No effects were observed at lower doses (≤400 mg/kg-day). Therefore, the NOAEL in this study in both rats and mice was 400 mg/kg-day.

In the chronic studies (NTP, 1989a), benzyl alcohol was administered by gavage 5 days/week, for 103 weeks to groups of 50 male and 50 female F344/N rats at 0, 200, or 400 mg/kg and B6C3F$_1$ mice at 0, 100, or 200 mg/kg for 2 years. The study featured comprehensive histopathological examination of the test animals. No effects, other than increased incidence of corpora amylacea, were clearly related to benzyl alcohol administration in either species. The NOAEL in rats and mice was 400 and 200 mg/kg-day, respectively, the highest dose tested in both species. The rat study, however, experienced a high incidence of accidental deaths, precluding a meaningful interpretation of the mortality data in this study.

Benzyl alcohol has been evaluated in several reproductive and developmental screening assays. Data on developmental and reproductive toxicity are limited to single dose-level studies in mice (York et al., 1988; Hardin et al., 1987). Benzyl alcohol administered at 550 mg/kg-day by gavage during 6–15 days of gestation produced no adverse effects (York et al., 1988). Hardin et al. (1987) reported both maternal toxicity and fetotoxicity in mice when exposed to 750 mg benzyl alcohol/kg-day during 6–13 days of gestation. This LOAEL is similar to the dose at which neurotoxicity was observed in both male and female rats exposed to 800 mg benzyl alcohol by gavage reported in the NTP (1989a) subchronic study. These studies are not adequate to derive p-RfD values because they do not evaluate a comprehensive set of developmental or reproductive toxicity parameters; however, the results of these assays suggest that maternal toxicity, rather than developmental and reproductive endpoints, may be a sensitive indicator of benzyl alcohol toxicity.

A subchronic p-RfD for benzyl alcohol can be derived based on the subchronic NTP (1989a) study in mice. This study identifies a LOAEL of 800 mg/kg-day and a NOAEL of 400 mg/kg-day in mice based on clinical signs of neurotoxicity, such as staggering, labored breathing, and lethargy in both males and females. The 400-mg/kg-day NOAEL is supported by the results of the chronic rat study, which found no treatment-related lesions in the brain or other tissues. The NOAEL/LOAEL approach was used to derive the p-RfD. The data provide no indication of the shape of the dose-response curve in this dose range and are not suitable for benchmark dose modeling (U.S. EPA, 1996, 2000). Although the high dose (800 mg/kg-day) reported in rats was associated with neurotoxicity and mortality, the NTP (1989a) reported

uncertainties in dose-response caused by gavage error; thus, the rat study is precluded for development of toxicity values.

The NOAEL in mice of 400 mg/kg-day was adjusted to a continuous exposure basis (400 mg/kg-day × 5 day/7 days = 286 mg/kg-day) and divided by a composite uncertainty factor of 1000 (UF_A = 10 [extrapolation from animal studies], UF_H = 10 [human variability], and UF_D = 10 [database deficiencies, including lack of adequately conducted reproductive and neurological toxicity tests]) to derive a subchronic p-RfD as follows:

Subchronic p-RfD = NOAEL ÷ UF
= 286 mg/kg-day ÷ 1000
= **0.3 or 3×10^{-1} mg/kg-day**

Confidence in the key study is low. The study evaluates a sufficient number of doses and animals per dose in two species (rats and mice), and a sufficient number of tissues appears to be evaluated. However, key studies have several other limitations, such as high mortality due to gavage error, poor documentation of microscopic examinations, and lack of clinical pathology evaluations. Confidence in the database is low. No supporting studies other than the ensuing chronic study were located, and adequate reproductive and neurological toxicity studies are not available. Because the brain was shown to be a target, it has not been established that the most sensitive toxicological endpoint has been adequately characterized. Therefore, confidence in the subchronic p-RfD is low.

The chronic NTP (1989a) study in mice provides a suitable basis for derivation of a chronic p-RfD for benzyl alcohol. This study provides a NOAEL of 200 mg/kg-day for effects on survival, growth, and tissue histopathology; a LOAEL is not identified. The mouse chronic study reported mineralization of thalamus in female mice and adenomas in adrenal cortex in high-dose males; these were within historical control incidence, and were therefore, not attributed to benzyl alcohol treatment. The mouse study has been chosen over the similar rat study, with a NOAEL of 400 mg/kg-day, as the critical study because the rat study is compromised by a high number of accidental deaths, precluding a meaningful interpretation of the mortality data from this study. The NOAEL in mice of 200 mg/kg-day has been adjusted to a continuous exposure basis (200 mg/kg-day × 5 days/7days = 143 mg/kg-day) and divided by a composite UF of 1000 (10 for interspecies extrapolation; 10 for human variability; and 10 for database deficiencies, which includes the lack of adequately conducted reproductive, developmental, and neurological toxicity tests). A chronic p-RfD is derived as follows:

Chronic p-RfD = NOAEL / UF
= 143 mg/kg-day / 1000
= **0.1 mg/kg-day or 1×10^{-1} mg/kg-day**

Confidence in the principal study is medium. Although the study authors performed a comprehensive histopathology examination, no effects clearly associated with benzyl alcohol administration are identified. Confidence in the database is low; supporting data for the critical study are available only from the subchronic study, and only limited information has been located on the potential of ingested benzyl alcohol to induce developmental or reproductive effects. Benzyl alcohol has been shown to affect the nervous system in rats and mice in the 13-week studies; however, a comprehensive neurological toxicity study has not been located.

Therefore, it has not been established that the most sensitive toxicological endpoint has been adequately characterized. Confidence in the chronic p-RfD is low.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR BENZYL ALCOHOL

No adequate human or animal data regarding the toxicity of benzyl alcohol following subchronic or chronic inhalation exposure are available, precluding derivation of p-RfC values.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR BENZYL ALCOHOL

There are no human carcinogenicity data for benzyl alcohol. Benzyl alcohol did not induce tumors in a 2-year study in male or female rats and mice (NTP, 1989a). The sensitivity of the studies to detect carcinogenicity may have been compromised by the lack of a maximum tolerated dose achieved in mice of both sexes. No toxic effects occurred in male or female mice at up to 200 mg/kg-day, and only mild toxic effects (staggering during the first two weeks of the study) occurred at 800 mg/kg-day in mice during the 13-week range-finding study. Also, mice appeared to be less sensitive than rats to benzyl alcohol toxicity in the 13-week study, and rats tolerated up to 400 mg/kg-day for 2 years. Therefore, it appears that mice could have been given substantially higher doses than 200 mg/kg-day for 2 years. Although a clear NOAEL is not observed in rats either, severe effects are noted in the 13-week range-finding study (NTP, 1989a) at a dose only 2-fold higher than the highest dose tested in the 2-year bioassay. Therefore, it appears that the maximum tolerated dose was approached in the rat study. Although not clearly related to treatment, survival is significantly reduced at both doses in female rats due to a large number of accidental deaths. However, the increased mortality in the treatment groups does not appear to substantially affect the sensitivity of the bioassay because survival rates at 12, 18, and 24 months were within U.S. EPA (1986) guidelines. NTP (1989a) considered survival to be adequate for cancer assessment. Benzyl alcohol has produced mixed results in genotoxicity assays; however, the data suggest that benzyl alcohol is not likely a potent genotoxic agent. Under the U.S. EPA (2005) cancer guidelines, there is "*Inadequate Information to Assess Carcinogenic Potential*" based on the available data.

Derivation of quantitative estimates (p-OSF or p-IUR) of cancer risk for benzyl alcohol is precluded by the absence of data.

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